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Status of vaccine research and development of vaccines for HIV-1☆

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ABSTRACT

Human immunodeficiency virus (HIV) is the cause of one of the most lethal pandemics in human history, although in recent years access to highly effective anti-retroviral therapy has provided new hope worldwide. Transmission of HIV by sexual contact, childbirth and injection drug use has been reduced, but 2 million are newly infected each year, and much of the transmission is from people who do not know their status. In addition to known methods, a preventive vaccine is needed to end the pandemic. The extraordinary mutability and genetic diversity of HIV is an enormous challenge, but vaccines are being designed for broad coverage. Computer-aided design of mosaic immunogens, incorporating many epitopes from the entire genome or from conserved regions aim to induce CD8+ T cells to kill virus-infected cells or inhibit virus replication, while trimeric envelope proteins or synthetic mimics aim to induce broadly reactive neutralizing antibodies similar to those cloned from some infected patients. Induction of more potent and durable responses may require new adjuvants or replicating chimeric vectors chimeras that bear HIV genes. Passive or genetic delivery of broadly neutralizing antibodies may provide broad protection and/or lead to insights for vaccine designers. Proof-of-concept trials in non-human primates and in one human efficacy trial have provided scientific clues for a vaccine that could provide broad and durable protection against HIV. The use of vaccines to destroy HIV reservoirs as part of therapy or cure is now also being explored.

Since the initial recognition of an acquired immunodeficiency syndrome (AIDS) in 1981 through the presentation of rare *Pneumocystis carinii* pneumonia among homosexual men in the USA, human immunodeficiency virus type 1 (HIV-1) has given rise to a pandemic of nearly unprecedented proportion, causing extensive global morbidity and mortality [1,2]. Because the virus targets an immune system that has evolved to fight such pathogens, AIDS is characterized by a progressive loss of HIV's preferred target, CD4+ T cells, and chronic immune activation resulting in an immunodeficiency syndrome that allows numerous opportunistic infections and cancers, typically leading to serious morbidity and mortality in the absence of treatment. Since 1981, over 70 million people have been infected with HIV resulting in 36 million deaths. UNAIDS estimates that, in 2014 alone, nearly 37 million persons were living with HIV, 2 million were newly infected, and 1.2 million died from their infection, most of whom were in sub-Saharan Africa [3]. HIV, although not as easily transmitted as some viruses, can be transmitted with varying efficiency by multiple modalities: *via* injection of blood or blood-derived products; from mother-to-child during pregnancy, at delivery or through breast-feeding; and most commonly through sexual intercourse [4]. Fortunately, significant research since the beginning of the epidemic has resulted in the development of more than 40 anti-retroviral drugs that in various combinations can help control the infection [5]. However, despite major gains in the numbers of HIV infected individuals accessing anti-retroviral therapy (ART) in recent years, in 2014 there were still 59% of HIV-positive adults and 68% of children without access to these life-saving medications and importantly, for every person enrolled in treatment, a new infection occurred [6]. This is particularly tragic because effective ART treatment almost eliminates the chance of onward transmission of HIV [7]. Ultimately, even with these significant advances in ART and additional prevention efforts, the development of a safe and effective HIV vaccine remains a global public health priority that is the best hope for preventing,

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controlling and ending the AIDS pandemic. Even if other treatment and prevention tools are extensively scaled up, modeling analysis shows that a 70-percent-efficacious AIDS vaccine with strong uptake could reduce new annual HIV infections in lower and middle income countries by 44% in 10 years and by 65% in 25 years, ultimately averting tens of millions of infections and saving millions of lives [8].

1. Biological feasibility for prophylactic vaccine development

Unlike many infectious diseases, HIV infection does not resolve and give rise to protective immunity against subsequent exposure. While some individuals remain uninfected despite multiple exposures to HIV-1, immune-mediated correlates of protection have not been conclusively identified. Adaptive immune responses against HIV are often directed toward the envelope (Env) protein on the surface of the virus and the capsid protein (Gag) that surrounds and protects the HIV RNA. In people who control virus replication and remain well for many years, Gag-specific CD8+ T cells can inhibit HIV-1 replication in *ex vivo*-infected cells, a phenotype not observed in those who become ill more quickly [9]. The contribution of cellular immunity to controlling infection has also been observed in simian immunodeficiency virus (SIV) challenge studies of rhesus macaques, although the correlates of protection are not well understood. Pre-clinical studies have shown that recombinant cytomegalovirus (CMV) vectored SIV vaccines induce CD8+ effector memory cells—some conventionally restricted by MHC class I and some unconventional cells—that control SIV to undetectable levels in approximately 50% of immunized macaques [10]. These studies are providing clues toward understanding how best to elicit cellular immune responses that will control and possibly abort HIV infection.

Despite the importance of eliciting a robust cellular immune response, most effective vaccines prevent infection by stimulating the development of neutralizing antibodies. About 5% of HIV infected individuals develop potent neutralizing antibodies against Env that effectively neutralize a broad range of HIV-1 isolates *in vitro* [11]. A number of broadly neutralizing human monoclonal antibodies (bNAbs) have been isolated and characterized in detail. *In vitro* experiments have shown that combinations of such bNAbs can prevent infection of human CD4+ T cells by virtually all HIV isolates. In animal models, passive transfer of several different bNAbs can prevent infection at antibody concentrations that should be achievable by vaccination [12]. The activity and specificity of bNAbs is currently guiding the design of immunogens to elicit broad virus neutralization.

2. Biological feasibility for therapeutic vaccine development

Therapeutic vaccines for HIV have been evaluated in the past with very limited and inconsistent success, when the model was vaccination during untreated HIV infection [13]. Recently, an alternative approach has been tested, which is to vaccinate patients on highly effective ART, in the hope of preventing virus escape once treatment is stopped or effecting a cure by removing virus reservoirs [14,15]. This approach will be hindered by the enormous variation of HIV within each infected person, but might hold promise if vaccines that induce sufficiently broad, potent and durable immune responses were employed.

3. General approaches to vaccine development for this disease for low and middle income country markets

Some two hundred HIV vaccine candidates/regimens have been clinically tested since 1986, yet efficacy trials were completed for only four vaccines [16], only one of which demonstrated modest efficacy in preventing HIV acquisition [17]. An Env subunit vaccine (gp120, VaxGen) formulated in an alum adjuvant failed to elicit antibodies that could neutralize most tested isolates or to prevent or control HIV infection. An adenovirus type 5 vector with a *gag-pol-nef* insert (Merck) not only failed to control HIV infection but transiently potentiated HIV acquisition for reasons that remain unclear. One possibility is that repeated vaccination with the Ad5 vector stimulated a generalized immune activation that then provided activated CD4+ target cells for HIV. More recently, a DNA prime boosted with an Ad5 vector delivering *gag-pol-nef* and three *env* genes (NIAID Vaccine Research Center) had no effect on HIV infection or viral load in those who became infected [18]. The most promising product, a prime-boost regimen of a Canarypox vector delivering *gag-pol-env* with a gp120 protein boost (ALVAC – Sanofi; gp120-Vaxgen), designed to elicit both cellular and humoral immunity, demonstrated for the first time that a vaccine could prevent HIV acquisition with 31.2% overall efficacy (RV144).

Once a safe and effective HIV vaccine is developed and licensed, decisions will have to be made regarding which populations to target for vaccination. There is general consensus that priority should be given to high risk groups exposed to HIV through sexual contact or injection drug use. Vaccination of infants has also been proposed and tested in previous early phase clinical studies, however ancillary treatment with drugs or passive antibodies would likely be needed to prevent infection initially, until the child's immune system responds to the vaccination [19,20].

4. Technical and regulatory assessment

HIV vaccine candidates are advanced on the basis of safety and immunogenicity data from animal models and from Phase I clinical trials. The primary HIV animal challenge models include Rhesus macaques challenged with either SIV or a chimeric construct of SIV and HIV Env (SHIV). The SIV or SHIV models are most often chosen based on the availability of appropriate reagents (HIV vaccine candidates made in an SIV version or a SHIV constructed to match the Env in the HIV vaccine candidate). The most common SIV strain used, mac239, is very difficult to neutralize and CD8+ T cells provide limited protection against this virus. SHIV constructs, however, are generally less virulent and are more easily neutralized by antibodies to HIV Env.

More than 250 HIV vaccine Phase I and II clinical trials have been conducted in more than 30 countries [16]. For an updated list of the status of candidates in current developement, please see Table 1. Although a clear correlate of protection remains elusive, through pre-clinical and clinical evaluation, it is presumed that the best vaccine candidates should elicit neutralizing antibodies, non-neutralizing antibodies that mediate viral clearance through other mechanisms (such as antibody-dependent cell-mediated cytotoxicity-ADCC or virus inhibition, ADCVI), and T cells (primarily CD8+) that suppress virus growth or kill virus-infected cells. For example, efficacy in the RV144 trial was associated with non-neutralizing IgG antibodies to the V1V2 region of Env [21]. To best predict correlates of vaccine efficacy in the absence of additional successful Phase III trials, we must turn to examples of virus control in HIV infected humans and protection from infection or disease in SIV or SHIV models. In humans, CD8+ T cells, particularly those directed at conserved regions of Gag, are correlated with control of virus replication [9,22]. The general consensus is that vaccine candidates should induce classical CD8+ T effector or effector memory cells (restricted by Class I MHC). Interestingly, however, some of the macaques that were protected from SIV challenge after vaccination with CMV vectors expressing multiple SIV antigens contained unconventional T effector cells [23]. Whether

Table 1
Development status of current vaccine candidates.

Candidate name/trial identifier	Class/antigen	Phase I	Phase IIa
Ad26.EnvA-01/**Ad26.ENVA.01**	Adeno/Ad26 Env A	X	
VRC-HIVADV038-00-VP; VRC-HIVADV027-00-VP/**VRC 012 (07-I-0167)**	Adeno/Ad35 Env A; Ad5 Env A	X	
VRC-HIVADV027-00-VP; VRC-HIVADV052-00-VP; VRC-HIVADV038-00-VP/**HVTN 083**	Adeno/Ad35 Env A; Ad5 Env A; Ad5 Env B	X	
Ad26.EnvA-01/Ad26.ENVA.01 Mucosal/**IPCAVD003**	Adeno/Ad26 Env A	X	
VRC-HIVADV014-00-VP/**VRC 015 (08-I-0171)**	Adeno/Ad5 Gag-Pol Env A/B/C	X	
Ad5HVR48.ENVA.01/**Ad5HVR48.ENVA.01**	Adeno/Ad5/Ad48 Env A	X	
VRC-HIVADV014-00-VP; VRC-HIVADV038-00-VP; VRC-HIVADV052-00-VP; VRC-HIVADV054-00-VP; VRC-HIVADV053-00-VP/**HVTN 085**	Adeno/Ad5 Gag-Pol Env A/B/C; Ad5 Env A; Ad5 Env B; Ad5 Gag-Pol B; Ad5 Env C	X	
rAd35 Env A; rAd5 Env A; rAd5 Env B/**HVTN 083**	Adeno/Env A, Env B	X	
VRC-HIVADV014-00-VP; VRC-HIVADV054-00-VP/**HVTN 084**	Adeno/Ad5 Gag-Pol Env A/B/C, Ad5 Gag-Pol B	X	X
MVA gag/pol/env mosaic inserts/**IPCAVD006**	Adeno and Pox/gag/pol/env mosaic	X	
ChAdV63.HIVconsv; MVA.HIVconsv; plus HCV vaccine/**PEACHI-04**	Adeno and Pox/ChimpAd63 consensus; MVA consensus	X	
PENNVAX-GP/**HVTN 098**	DNA/Gag, Pol, Env B		
VRC-HIVDNA016-00-VP; VRC-HIVADV014-00-VP/**HVTN 076**	DNA and Adeno/DNA Gag, Pol, Nef B, env A,B,C; Ad5 Gag-Pol Env A/B/C	X	
VRC-HIVDNA044-00-VP; VRC-HIVADV027-00-VP; VRC-HIVADV038-00-VP/**HVTN 077**	DNA and Adeno/DNA Env A; Ad35 Env A; Ad5 Env A	X	
VRC-HIVDNA016-00-VP; VRC-HIVADV014-00-VP/**HVTN 082**	DNA and Adeno/DNA Gag, Pol, Nef B, Env A,B,C; Ad5 Gag-Pol Env A/B/C	X	
DNA Nat-B env; DNA CON-S env; DNA Mosaic env; MVA-CMDR/**HVTN 106**	DNA and Pox/DNA Nat-B env; DNA CON-S env; DNA Mosaic env; MVA Gag-Pol, Env E	X	
DNA-HIV-PT123; NYVAC-HIV-PT1; NYVAC-HIV-PT4/**HVTN 092** -01	DNA and Pox/DNA Gag, Env, Pol-Nef C; NYVAC Gag, Env, Pol-Nef C	X	
MVA-CMDR; Pennvax-G/**RV262**	DNA and Pox/MVA Gag-Pol, Env E; DNA Env A,C,D, Gag consensus	X	
GEO-D03; MVA/HIV62/**HVTN 094**	DNA and Pox/DNA Gag, PR, RT, Env, Tat, Rev, Vpu B; MVA Gag, Pol Env B	X	
HIVIS-DNA; MVA-CMDR/**TaMoVac II**	DNA and Pox/DNA env, rev, gag, and RT A/B/C, MVA Gag-Pol, Env E		X
HIV-MAG; VSV-Indiana HIV gag vaccine/**HVTN 087**	DNA and Replicating Vector/DNA Gag, Pol, Nef Tat, Vif, Env B; Replicating VSV Gag	X	
Tiantan vaccinia; Chinese DNA/**Tiantan vaccinia HIV Vaccine and DNA**	DNA and Replicating Vector/Replicating tiantan Gag, Pol, Env B'/C; DNA Gag, Pol, Env B'/C		X
pSG2.HIVconsv DNA, MVA.HIVconsv and Ad35-GRIN/**IAVI N004/HIVCORE004/IPCAVD009**	DNA, Adeno and Pox/MVA consensus; DNA consensus; Ad35 Gag, RT, Integ, Nef A	X	X
MVA.HIVconsv; pSG2.HIVconsv; ChAdV63.HIVconsv/**HIV-CORE002**	DNA, Adeno and Pox/MVA consensus; DNA consensus; ChimpAd63 consensus	X	
LIPO-5; MVA-B; GTU-MultiHIV/**VRI01**	DNA, Pox, Protein/Protein Gag, Nef, Pol B; MVA Nef; Gag; Pol B; DNA Rev, Nef, Tat, Pol, Env B	X	X
SAAVI DNA-C2; SAAVI MVA-C; Oligomeric gp140/MF59/**HVTN 086, SAAVI 103**	DNA, Pox, Protein/DNA Gag, RT, Tat, Nef, Env C; MVA Gag, RT, Tat, Nef, Env C; Protein Env	X	
DNA - CN54ENV and ZM96GPN; CN54gp140; MVA-C/**UKHVCSpoke003**	DNA, Pox, Protein/DNA Gag, Pol, Nef C, MVA Gag, Pol, Nef C, Protein Enc C	X	
MVA-CMDR/**RV 365**	Pox/MVA Gag-Pol, Env E	X	
ALVAC-HIV vCP1521; AIDSVAX B/E/**RV 306**	Pox and Protein/Canarypox Env B,E; Protein Env B,E		X
ALVAC-HIV vCP1521; AIDSVAX B/E/**HVTN 097**	Pox and Protein/Canarypox Env B,E; Protein Env B,E	X	
ALVAX pox prime with protein boost and MF59/**HVTN 100**	Pox and Protein/Canarypox Env B,E; Protein Env B,E	X	X
ALVAC-HIV vCP1521; AIDSVAX B/E/**RV 305**	Pox and Protein/Canarypox Env B,E; Protein Env B,E		X
Trimeric gp140/**IPCAVD008**	Protein/gp140	X	
CN54gp140/**CN54gp140 mixed with GLA-AF**	Protein/Env C	X	
AIDSVAX®B/E; DNA-HIV-PT123/**HVTN 105**	Protein and DNA/DNA: clade C ZM96 Gag and gp140, CN54 Pol-Nef. Protein: clade B (MN) HIVgp120 glycoprotein clade E (A244) HIV gp120 glycoprotein	X	
AIDSVAX®B/E; DNA-HIV-PT123/**IDEA EV06**	Protein and DNA/DNA: clade C ZM96 Gag and gp140, CN54 Pol-Nef. Protein: clade B (MN) HIVgp120 glycoprotein clade E (A244) HIV gp120 glycoprotein	X	
AIDSVAX B/E/**RV 328**	Protein/Env B,E		X
Ad26/**R001**	Replicating Vector/Ad26 Env	X	
Ad4-EnvC150; Ad4-mgag/**PXVX-HIV-100-001/HVTN 110**	Replicating Vector/Replicating Ad4 Env C; Replicating Ad4 Gag	X	
VSV-Indiana HIV gag vaccine/**HVTN 090**	Replicating Vector/Replicating VSV Gag	X	
eV-G; Ad35-GRIN/**IAVI S001**	Replicating Vector and Adeno/Sendai Gag A; Ad35 Gag, RT, Integ, Nef A	X	
AAV1-PG9/**IAVI A003**	Vectored Immunoprophylaxis/AAV1 vectored PG9	X	
VRC-01/**IMPAACT P1112**	Immunoprophylaxis/VRC-01 antibody	X	

these unconventional responses will also be effective in controlling HIV in humans remains to be seen.

Phase III HIV vaccine efficacy trials have enrolled a heterogeneous array of populations, including men who have sex with men, injection drug users, heterosexual men and women at high risk for HIV infection, and members of the general population from across global regions in the Americas, South Africa and Thailand. As other proven non-vaccine prevention methods, such as treatment-as-prevention, voluntary medical male circumcision and pre-exposure prophylaxis with antiretroviral drugs become more widely available, it will be more difficult to find appropriate at-risk individuals for vaccine trials, and questions may be raised about the standard of preventive interventions that is required in these trials. Consultation with involved communities

will be essential, as emphasized in UNAIDS Good Participatory Practices Guidelines (http://www.unaids.org/sites/default/files/media_asset/JC1853_GPP_Guidelines_2011_en_0.pdf).

5. Status

As an outcome of the RV-144 efficacy trial, the Pox-Protein Public Private Partnership, consisting of Sanofi, Novartis, NIAID, Bill & Melinda Gates Foundation, the Military HIV Research Program (MHRP) and the HIV Vaccine Clinical Trials Network, is planning a next phase of efficacy trials that may test the RV144 vaccine regimen in a population of men who have sex with men in Thailand and in heterosexual populations in sub-Saharan Africa [24]. These trials may add additional booster immunizations and more potent adjuvants aimed at extending the durability of protection. If vaccine efficacy of >50% is demonstrated, a licensure application in South Africa is possible as early as 2021. In addition, test of concept efficacy trials are now under consideration for prime-boost regimens utilizing next generation pox vectors (NYVAC; Sanofi), gp120 boosters (Novartis), and DNA (IPPOX Foundation, VICAL) in adaptive clinical trials.

Parallel efforts are developing vaccine candidates addressing the hyper-variability of HIV, aimed at increasing breadth of antibody and T cell responses or focusing responses to conserved regions of the virus. For example, vaccines based on two different hypotheses to elicit broad cellular immune responses are in development. One focuses immune responses to those regions of HIV that are highly conserved and therefore may be required for viral replicative fitness (Oxford University, IAVI, EDCTP) [25], while the other, termed "mosaic antigens" use *in silico* methods (Los Alamos National Laboratories) to design immunogens that represent diverse sequences representing the optimal choice of epitopes from all known HIV strains, for broad coverage of circulating viruses (Johnson and Johnson/Janssen, Beth Israel Deaconess Medical Center, NIAID, Ragon Institute) [26].

Recent technological advances in B cell immunology, next generation sequencing, bioinformatics and structural biology have facilitated the generation of many potent bNAbs. Studies have identified bNAb binding sites on HIV Env, solved structural characterization of Env trimer and Env epitopes with atomic-level precision, and provided a better understanding of the ontogeny of bNAbs in HIV infected individuals [27]. Designing immunogens to elicit these bNAbs remains a major challenge, however, though structural design is now beginning to yield more stable and potent immunogens [28]. bNAbs are also being evaluated for passive prophylaxis and treatment, in phase I-II clinical trials (NIH Vaccine Research Center, Rockefeller University, MHRP) [29], and for delivery by gene transfer using adeno-associated virus vectors (Children's Hospital of Philadelphia, IAVI) in a phase I trial [30]. Finally, since the RV-144 trial showed that HIV acquisition could be prevented without bNAbs or robust CD8+ cellular immune responses, studies are ongoing to develop vaccines that elicit antibodies that work through other effector mechanisms, such as Fc-mediated interactions with the innate immune system [31].

Since the HIV vaccine field likely will not see data emerging from the next set of efficacy trials until 2019–2020, current strategies are focused on advancing leading candidates through clinical development, improving vaccine delivery methods and optimizing the next generation of candidates entering clinical development. These include:

- HIV Env Trimers: Recent resolution of the structure of a stabilized HIV Env trimer will lead to clinical evaluation of immunogens more closely mimicking the native Env glycoprotein.
- HIV Antibody Epitope Based Vaccines: Recent elucidation of at least five major epitopes on HIV Env that bind bNAbs will lead to the generation of clinical candidates targeting each of these epitopes, including glycopeptides (see also below), computationally derived scaffolds and novel immunogens designed to bind to putative germline ancestors of the bNAbs.
- Sequential Immunization with Different Immunogens: Increased understanding of how bNAbs evolve along with virus evolution in the human host will lead to testing the hypothesis that sequential immunization with different immunogens may be required to drive antibody affinity maturation.
- Conserved/Mosaic Hybrids: Next generation immunogens to elicit broad cellular immune responses will take advantage of the attributes of both conserved and mosaic antigens to drive breadth, depth and enhanced coverage of cellular immune responses by immunization.
- Replication Competent Viral Vectors: Replicating adenovirus, poxvirus, vesiculostomatitis virus and Sendai virus vectors are in preclinical and early clinical development. Research in this area will focus on vectors generating persistent infection, mucosal delivery, and targeting of the gut-associated lymphoid tissues all in hope of mimicking the efficacy of a live attenuated vaccine.
- Antigen Presentation Systems and Novel Adjuvants: Several virus-like particle and nanoparticle antigen presentation systems and novel adjuvants are in development. They are based on advances in understanding of innate and adaptive immune linkages.
- Synthetic Biology Technologies: Novel DNA and RNA vaccines are being explored in efforts to achieve the efficacy of viral vectors while mitigating concerns of anti-vector immunity. Delivery of such genetic vaccines by electroporation has shown promise in clinical trials.
- Glycobiology: Advances in glycobiology are yielding important insights for HIV vaccine research, both in characterization and synthesis of targets recognized by bNAbs, and in strategies to manipulate vaccine-induced Fc-mediated immune responses such as ADCVI and ADCC.

6. Financing the development of an HIV vaccine

HIV vaccine R&D is funded by the public and private sector [32]. In 2014, 841 million USD was available, invested in basic research (29%), preclinical research (33%), clinical research (34%), and other (4%). Funding over the last several years has flat-lined, and is increasingly vulnerable due to its dependency on just two major sources: 84% of funding comes from the US government and the Bill and Melinda Gates Foundation. Over the next 5–10 years, it will be essential for funding to respond to the global pipeline, notably the planned efficacy studies and efforts to leverage new knowledge, such as in the bNAb domain, to design and evaluate novel vaccine approaches.

For HIV vaccines that ultimately reach the state of licensure, initiatives such as The Vaccine Alliance GAVI can help to ensure broad roll-out and access in countries and populations most affected by HIV/AIDS. HIV vaccines, notably those with a high level of efficacy and broad coverage (across HIV variants) will likely be very cost-efficient, especially when considered against the cost of life-long antiretroviral treatment. Modeling studies indicate that a preventive HIV vaccine could dramatically reduce the number of new infections even if coverage is less than 50% in low- and middle-income countries [33]. A preventive vaccine could be especially beneficial for people who are unable to access or consistency use current methods for preventing HIV infection, due to barriers or dependency on compliance or behavioral change. The best hope for ending the AIDS pandemic is to develop an effective, accessible

vaccine that is delivered in the context of a comprehensive prevention strategy.

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References

[1] Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981;305(24):1425–31.
[2] Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, et al. An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med 1981;305(24):1431–8.
[3] Joint United Nations Programme on HIV/AIDS (UNAIDS). How AIDS Changed Everything: 2015 Global Statistics Fact Sheet. Genenva, Switzerland; 2015. http://www.unaids.org/en/resources/campaigns/HowAIDSchangedeverything/factsheet [accessed 26.07.15].
[4] Kuritzkes DR, Koup RA. Human immunodeficiency viruses. In: Knipe DM, Howley PM, editors. Fields virology. 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2013. p. 1561–83.
[5] U.S. Food and Drug Administration. Antiretroviral drugs used in the treatment of HIV infection. http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm118915.htm [accessed 26.07.15].
[6] How AIDS Changed Everything: MDG 6: 15 Years, 15 Lessons of Hope from the AIDS Response. Joint United Nations Programme on HIV/AIDS. http://www.unaids.org/en/resources/documents/2015/MDG6_15years-15lessonsfromtheAIDSresponse [accessed 27.07.15].
[7] Cohen MS, McCauley M, Gamble TR. HIV treatment as prevention and HPTN 052. Curr Opin HIV AIDS 2012;7(2):99–105.
[8] Harmon TM, Fisher KA, McGlynn MG, Stover J, Warren MJ, Teng Y, et al. Exploring the Potential Health Impact and Cost-Effectiveness of AIDS Vaccine within a Comprehensive HIV/AIDS Response in Low- and Middle-Income Countries. PLoS ONE 2016;11(1):e0146387.
[9] Walker BD, Yu XG. Unravelling the mechanisms of durable control of HIV-1. Nat Rev Immunol 2013;13(7):487–98.
[10] Hansen SG, Ford JC, Lewis MS, Ventura AB, Hughes CM, Coyne-Johnson L, et al. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. Nature 2011;473(7348):523–7.
[11] Simek MD, Rida W, Priddy FH, Pung P, Carrow E, Laufer DS, et al. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm. J Virol 2009;83(14):7337–48.
[12] Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, et al. A Blueprint for HIV Vaccine Discovery. Cell Host Microbe 2012;12(4):396–407.
[13] Girard MP, Koff WC. Human immunodeficiency virus vaccines. In: Plotkin SA, Orenstein W, Offit PA, editors. Vaccines. 6th ed. Philadelphia, PA: Sanders; 2012. p. 1097–121.
[14] Autran B. Toward a cure for HIV-Seeking effective therapeutic vaccine strategies. Eur J Immunol 2015;45(12):3215–21.
[15] Mylvaganam GH, Silvestri G, Amara RR. HIV therapeutic vaccines: moving towards a functional cure. Curr Opin Immunol 2015;35:1–8.
[16] International AIDS Vaccine Inititaive (IAVI) Clinical Trials Database. IAVI. www.iavi.org [accessed 27.07.15].
[17] Schiffner T, Sattentau QJ, Dorrell L. Development of prophylactic vaccines against HIV-1. Retrovirology 2013;10:72.
[18] Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med 2013;369(22):2083–92.
[19] Fouda GG, Cunningham CK, Permar SR. Infant HIV-1 vaccines: supplementing strategies to reduce maternal-child transmission. JAMA 2015;313(15):1513–4.
[20] Safrit JT. HIV vaccines in infants and children: past trials, present plans and future perspectives. Curr Mol Med 2003;3(3):303–12.
[21] O'Connell RJ, Excler JL. HIV vaccine efficacy and immune correlates of risk. Curr HIV Res 2013;11(6):450–63.
[22] Mothe B, Hu X, Llano A, Rosati M, Olvera A, Kulkarni V, et al. A human immune data-informed vaccine concept elicits strong and broad T-cell specificities associated with HIV-1 control in mice and macaques. J Transl Med 2015;13:60.
[23] Hansen SG, Sacha JB, Hughes CM, Ford JC, Burwitz BJ, Scholz I, et al. Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms. Science 2013;340(6135):1237874.
[24] Excler JL, Tomaras GD, Russell ND. Novel directions in HIV-1 vaccines revealed from clinical trials. Curr Opin HIV AIDS 2013;8(5):421–31.
[25] Borthwick N, Ahmed T, Ondondo B, Hayes P, Rose A, Ebrahimsa U, et al. Vaccine-elicited human T cells recognizing conserved protein regions inhibit HIV-1. Mol Ther 2014;22(2):464–75.
[26] Barouch DH, Stephenson KE, Borducchi EN, Smith K, Stanley K, McNally AG, et al. Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys. Cell 2013;155(3):531–9.
[27] Sattentau QJ. Immunogen design to focus the B-cell repertoire. Curr Opin HIV AIDS 2014;9(3):217–23.
[28] Jardine JG, Ota T, Sok D, Pauthner M, Kulp DW, Kalyuzhniy O, et al. HIV-1 VACCINES. Priming a broadly neutralizing antibody response to HIV-1 using a germline-targeting immunogen. Science 2015;349(6244):156–61.
[29] Caskey M, Klein F, Lorenzi JC, Seaman MS, West Jr AP, Buckley N, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature 2015;522(7557):487–91.
[30] Schnepp BC, Johnson PR. Adeno-associated virus delivery of broadly neutralizing antibodies. Curr Opin HIV AIDS 2014;9(3):250–6.
[31] Forthal D, Hope TJ, Alter G. New paradigms for functional HIV-specific nonneutralizing antibodies. Curr Opin HIV AIDS 2013;8(5):393–401.
[32] HIV Prevention Research & Development Funding Trends, 2000–2014. HIV Resource Tracking Working Group; 2015. http://www.hivresourcetracking.org/ [accessed 27.07.15].
[33] The potential impact of an AIDS vaccine in low- and middle-income countries. IAVI Policy Brief; 2012. http://www.iavi.org/publications/file/70-the-potential-impact-of-an-aids-vaccine-in-low-and-middle-income-countries [accessed 27.07.15].